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(54) Abstract Title: **Therapeutic composition for respiratory delivery**

(57) A therapeutic composition in solid dose form comprising a mixture of first amorphous or non-crystalline microparticles comprising a bioactive agent and second amorphous non-crystalline microparticles comprising the same or a different bioactive agent, wherein the first microparticles are from 0.1 to 10 μ m in diameter and the second microparticles are from 10 to 100 μ m. Thus the microparticles are delivered via the nasal route to provide deep lung penetration (smaller microparticles) and deposition in the nasal cavity (larger microparticles). The bioactive agent may be an immunogen, particularly attenuated bacteria or virus, or an immunogenic peptide/protein. The glassy microparticles may be formed of hydrophobic derivatised carbohydrate (HDC). The therapeutic composition of the invention may be delivered by a nasal insufflator.

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THERAPEUTIC COMPOSITION FOR RESPIRATORY DELIVERYField of the Invention

This invention relates to therapeutic compositions, and in particular powders for delivery to the respiratory tract.

5 Background of the Invention

The respiratory tract is being investigated widely as a route of delivery for biopharmaceuticals, in particular peptides, proteins as well as vaccines. Indeed, many candidate therapeutic agents are being administered for topical or systemic effects. Often, the bioactive agent in question is formulated in a solid 10 dose form suitable for delivery to the lung via oral inhalation. Others are presented as powders for administration to the nasal cavity.

Solid delivery systems for controlled release are described in WO-A-9603978 (the content of which is incorporated herein by reference). Such compositions comprise an active agent and a glassy vehicle composed of a 15 stabilising polymer or hydrophobic derivatised carbohydrate (HDC).

EP-A-0678035 discloses a vaccine preparation in a controlled-release formulation. The vaccine is prepared by spray drying an immunogen adsorbed to an aluminium salt adjuvant, to form a free-flowing powder. The vaccine is then administered to a patient in the form of a liquid suspension via the parenteral 20 route. In one embodiment, the vaccine composition comprises at least one immediate-release vaccine preparation and at least one controlled-release vaccine preparation. The controlled-release preparation is formulated using a biodegradable polymer, including polyesters, polyanhydrides, cyanoacrylates and homopolymers of polylactic acids.

25 The need to form the liquid suspension for injection is problematic, especially if the vaccine is to be used in remote regions, where sterile water is difficult to prepare.

The nasal route is an attractive alternative to conventional oral or parenteral drug delivery. The two main disadvantages of nasal delivery are the 30 limited maximum dose per 'puff' and the rapidity of clearance from the nasal cavity.

Medicaments that are commonly delivered topically to the nasal cavity include decongestants, anti-histamines, cromoglycates, steroids and antibiotics. Medicaments that can also be systemically delivered through the nasal pathway, include hormones, for example, oxytocin and calcitonin, and analgesics, such as

5 anti-migraine compositions, as the high blood flow and large surface area of the nasal mucosa advantageously provides for rapid systemic uptake.

Nasal delivery is also expected to be advantageous for the administration of medicaments requiring a rapid onset of action, for example, analgesics, anti-emetics, insulin, anti-epileptics, sedatives and hypnotics, and also other

10 pharmaceuticals, for example, cardiovascular drugs.

Lehner *et al.*, *Nature Med.*, 1996; 2: 767-775 discloses that systemic immunisation, capable of protecting against a systemic infection, may not protect against a mucosal infection. Accordingly, there is a need for improvements in vaccine technology to protect against mucosal infection.

15 Summary of the Invention

According to a first aspect of the present invention, a therapeutic composition in solid dose form comprises a mixture of first amorphous or non-crystalline microparticles comprising a bioactive agent and second amorphous or non-crystalline microparticles comprising the same or different bioactive

20 agent. The first microparticles are of a size from 0.1 to 10 μm in diameter, preferably 0.5 to 5 μm , more preferably 1 to 3 μm . The second microparticles are of a size from 10 to 1000 μm , preferably 20 to 500 μm , preferably 25 to 100 μm .

The present invention utilises different sized microparticles to be

25 delivered together, via the nasal route, to provide both deep lung penetration and deposition in the nasal cavity. An advantage of the dual microparticulate population is the improvement in flow properties, whereby the larger 'nasal' particulates act as a 'carrier' for the alveolar powder much in the same way as lactose behaves in DPIs.

30 According to a second aspect of the invention, the present invention provides a single dose stabilised vaccine which contains glassy microparticles comprising the same or different antigens, whereby first microparticles present

the antigen rapidly (a so-called "priming" effect) and second microparticles present the antigen in a controlled manner (sustained, delayed or pulsatile manner) over a protracted time period ("boost" effect).

According to a further aspect of the invention, a device for delivering a
5 bioactive agent to a patient comprises a composition described above e.g., administered as a fine suspension using a spray device or if in the form of a powder using a powder device or nasal insufflator. Such devices are familiar to those skilled in the art.

According to the FDA guidelines, the design of nasal drug delivery
10 devices is aimed at achieving improved drug distribution whilst limiting the deposition of particles outside the target sites. However, according to this invention, surprising advantages can be demonstrated when optimising delivery to both the nasal "target site" and those outside, especially the alveolar region of the deep lung.

15 The nasal delivery technique of the present invention allows for delivery to the olfactory region, which represents the only region where it is possible to circumvent the blood-to-brain barrier (BBB) and enable communication with the cerebrospinal fluid (CSF) and the brain. Thus, the nasal delivery technique of the present invention may prove more effective than existing techniques in the
20 treatment of many common neurological diseases, such as Alzheimer's, Parkinson's, psychiatric diseases and intracerebral infections.

It is expected also that the nasal delivery technique of the present invention will allow for the more effective delivery of vaccines.

Description of the Invention

25 The present invention makes use of known products to formulate the first and second microparticles, to provide different sized microparticles to achieve the different delivery profiles.

Therapeutic compositions of the invention are said to be in "solid dose" form. The compositions are therefore solids, not solutions. Although the
30 preferred embodiment is a dry powder composition, where the first and second microparticles are administered in this form, the invention also contemplates the

presentation of the microparticles in an aqueous or non-aqueous medium for subsequent delivery. The microparticles will preferably be solids in suspension.

The microparticles are defined as "amorphous or non-crystalline". Those terms are familiar in the art, and methods for establishing whether a structure is 5 amorphous or non-crystalline are known. For example optical microscopy can be used, as will be appreciated by the skilled person.

"Nasal delivery" is defined as the administration of a composition via the nostril into the nasal cavity. This includes deposition on the olfactory, respiratory and vestibular mucosal surfaces as well as the sinuses.

10 "Lung delivery" is defined as the deposition of a composition in the lower respiratory tract, including the oro-pharyngeal and tracheo-bronchial regions, particularly, the lower airways including the alveolar sacs.

In one embodiment of the invention, a rapidly devitrifying HDC is used as the "primer" vehicle and a slower or non-vitrifying HDC is used as the controlled 15 release (CR) matrix for the "booster" fraction (a so-called prime-boost method). Suitable HDCs (including TOAc, i.e. trehalose octaacetate) are described in WO-A-9603978, WO-A-9829097 and WO-A-9933853, the content of each being incorporated herein by reference.

Alternatively, the vehicle of the primer particles may be a stabilising polyol 20 (SP). The booster fraction may also be SP-based but further contain a CR glass, such as PLAV/PLGA, etc. Exemplary hydrophobic biodegradable polymers which may be used in the present invention include poly(lactide-co-glycolide)(PLGA), polyglycolide(PGA), polylactide(PLA), copolyoxalates, polycaprolactone, poly(lactide-co-caprolactone), polyesteramides, polyorthoesters, poly(β -25 hydroxybutyric acid), and polyanhydride; while PLGA and PLA are preferred. Again, such components are described in WO-A-9603978. For example, suitable stabilising polyols include carbohydrates. The carbohydrates include monosaccharides, disaccharides, oligosaccharides and their corresponding sugar alcohols. Typically the SP will have a glass transition temperature (Tg) 30 greater than 30°C, preferably greater than 40°C and more preferably greater than 50°C. Preferred SPs include trehalose, sucrose and raffinose.

One advantage of the prime-boost method is its potential to induce at least additive immune responses. For instance, the simultaneous or subsequent administration of subunit antigens (boost) with pox-based vaccines (prime) results in complementary immune responses that include the induction of CTL 5 activity, neutralising antibody, proliferative responses (an indicators of T-cell help) and antibody-dependent cytotoxic activity (ADCC). Further, memory T-lymphocytes can mobilise rapidly and clone themselves if a specific antigen, encountered during infection or vaccination, appears at a later time.

Multivalent vaccines may be prepared by presenting more than one 10 antigen in the same primer microparticles or simply by delivering a mixture of priming microparticulates. The converse may also apply to the booster microparticulate fraction.

In a further embodiment, a SP-based primer fraction may be mixed with 15 a CR HDC-based fraction, to elicit the same effect. Conversely, the rapid release fraction may be HDC-based, e.g. TOAc, whilst the booster microparticles comprise SP/PLA/PLGA, etc.

Such a blend may be delivered as a unit dose via various routes of administration (see WO-A-9603978 for illustrative examples). This vaccine 20 delivery format may also provide an additive or synergistic immune response. It may also provide systemic and mucosal immunity. Thus, the invention can take advantage of the fact that the route of entry for many pathogens is by way 25 of mucosal surfaces, and immunity at such sites can limit or even prevent infection. There is also evidence that the mucosal immune system is inter-linked whereby, following mucosal immunisation, immunity is evident at a mucosal site some distance from the actual site of administration. Thus, pulmonary 30 administration of say, a herpes virus vaccine, may provide vaginal mucosal defence against the sexually transmitted form of the disease. Indeed, the invention takes advantage of presenting the antigen(s) simultaneously to the specific lymphoid tissues which process antigens presented on mucosal surfaces. The general term for such tissues is MALT (mucosally-associated lymphoid tissue) which comprises both bronchial (BALT) and nasal (NALT) subsets. This vaccination strategy would be ideal for all pathogens that are

carried as aerosols, especially bacteria and viruses and also allergens such as pollen.

Such a prophylactic delivery system may provide a "prime-boost" effect. However, a similar "load-sustain" pharmacological response may be achieved 5 from such a delivery system comprising a therapeutic bioactive.

In another embodiment, the two particle populations may comprise the same (homologous) or different (heterologous) antigen for delivery to both the nose and lung.

In a further embodiment, the particle composition of the invention may be 10 administered as a suspension in an aqueous or non-aqueous vehicle (e.g. perfluorocarbon) and delivered via the nose with the aid of an atomiser, nebuliser or other such devices known in the art. Alternatively, the suspension may be formulated in a conventional pMDI.

In a preferred embodiment, the compositions are adapted for mucosal 15 delivery, and delivered to the patient using known dry powder and liquid delivery systems (e.g. nebulisers and pMDI). Suitable dry powder inhalation devices are known in the art, including inhalators and insufflators. In this context, the compositions are formulated as dry powders, and may optionally include suitable carriers as is known in the art. For example, sugars, including lactose and 20 mannitol having a particle size of from 25 μm to 500 μm , preferably 50 to 250 μm in diameter are known in the art. However, the improved flow properties and delivery efficiency of blends according to this invention may negate the need for such carriers. The inspiratory manoeuvre is also important such that low flow rates combined with breath holding, enhance deposition at the desired regions 25 of the respiratory tract. Suitable inspiratory flow rates are <60 l/min, preferably <30 l/min, more preferably <15 l/min.

In the most preferred embodiment, the two particle populations have different densities. Preferably, the smallest fraction is also the least dense fraction, which will aid its passage through the nasal pathway and into the lower 30 respiratory tract. Preferably, the density is <0.4 g/cm³, more preferably <0.1 g/cm³. A preferred method of manufacture is via spray drying of a solution of emulsion to obtain the dried, low density microparticles as described in US

5874064 and WO-A-99/16419. The most preferred method is via spray freeze-drying. Conversely, the larger particle population of the composition is the most dense, thus aiding in its retention and impaction within the nasal cavity. Preferably, the density is >0.4 g/cm³, more preferably >1 g/cm³. Suitable methods of manufacture include spray drying with the aid of a rotary atomiser, as described in PCT/GB99/02930.

10 The products of the invention may be formulated using any known technique. Preferred methods include milling, spray drying, freeze drying, air drying, vacuum drying, fluidised-bed drying, spray freeze drying, co-precipitation and super critical fluid processing (including GAS, RESS and SEDS).

15 A formulation of the invention that comprises an antigen preferably also comprises an adjuvant. An adjuvant effect may be provided by a HDC. Examples of HDCs having different dissolution rates *in vivo* are TOAc and trehalose octapivalate and the adjuvant effect is related to their relative insolubility. Other suitable adjuvants include, but are not limited to, aluminium salts, squalene mixtures, muramyl peptide, saponin derivatives, cholera toxin B, mycobacterium cell wall preparations, immunostimulating complexes (ISCOMs) and nonionic block copolymer surfactants. For veterinary use, mitogenic components of Freund's adjuvant can be used. Also usable as adjuvants are 20 oligodeoxynucleotides containing CpG motifs (AM Krieg & HL Davis, *Curr. Opin. Mol. Ther.* 3 (1), 2001, pp 15-24) and these adjuvants are especially preferred when the antigen comprises polypeptides. The compositions may be formulated to include other components that aid mucosal delivery. For example, mucoadhesive agents, including cellulose and its derivatives, starch, carbopol, 25 poloxamers, chitosan and its derivatives and hyaluronic acid, may be incorporated into or around the microparticles of either/or/both populations, to aid retention at the mucosal surface.

30 Absorption enhancing materials may also be present in either/or/both particle populations. Suitable materials include, phospholipids, chelating agents, mucolytics, peptide inhibitors, and surface active agents selected from the group consisting of bile salts, fatty acids, fatty acid salts, acylglycerols, tyloxapols, acylcamitine, fusidates, and mixtures thereof.

Although described above with reference to vaccines, the microparticles may be formulated with any suitable bioactive agent. The term "bioactive" is intended to include any pharmacologically active agent, useful for treatment or prophylaxis. Example bioactive agents include, but are not limited to, peptides 5 or proteins, hormones, analgesics, anti-migraine agents, anti-coagulant agents, narcotic, antagonists, chelating agents, anti-anginal agents, chemotherapy agents, sedatives, compounds for the treatment of Alzheimer's disease (amyloid β or fragments thereof), anti-neoplastics and cardiovascular drugs. Preferred bioactive agents include insulin, erythropoietin (EPO), interferons, somatotropin, 10 somatostatin, tissue plasminogen activator (TPA), anti-malarial compounds, growth hormone releasing hormone, factor VIII and interleukins.

As stated previously, antigens (immunogens) are particularly preferred. Suitable antigens (immunogens) will be apparent to the skilled person and include live and attenuated viruses, nucleotide vectors encoding antigens, 15 bacteria, antigens, antigens plus adjuvants and haptens coupled to carriers. The antigens may be used in the prophylaxis of any bacterial or viral disease. For example, the antigen may be for the prevention of meningococcal disease (meningitis, septicaemia, meningoccaemia and pneumonia). In this embodiment, the antigen may be used to prevent infection of meningococci of any of groups 20 A, B, C, Y, W135, X and Z.

Preferred antigens are selected from the group consisting of diphtheria, tetanus, pertussis, botulism, cholera, Dengue, hepatitis A, B, C and E, hemophilus influenza B, herpes virus, *Hylobacterium pylori*, influenza, Japanese encephalitis, measles, mumps, papilloma virus, pneumococci, polio, rubella, 25 rotavirus, respiratory syncytial virus, *Shigella*, tuberculosis, yellow fever and combinations thereof.

Other suitable antigens for use in the practice of the invention include vaccines against anthrax (protective antigen), plague, small pox, tularaemia, melioidosis, Q fever, botulism, brucellosis, ricin, salmonella and staphylococcal 30 Enterotoxin B.

Viral particles useful in the preparation of vaccines are known and are applicable to the invention. The invention may be used for the prophylaxis of HIV, HepB, CMV and TB.

In an alternative embodiment of the invention, a unit dose inhalation powder, for therapy of diabetes, comprises a rapid-acting insulin fraction (pure or stabilised in a trehalose glass) together with a CR fraction comprising HA (or HA/HPC or Zn-complexed insulin embedded in HA). In this way, a meal-time insulin dose may be provided by the rapidly soluble component with basal plasma insulin being provided via the CR fraction. This may be applicable to a number of delivery routes and with the same excipient formats described above.

The following Examples illustrate the invention.

Example 1

A dry powder blend of first and second microparticles is prepared as follows:

15 'Lung' Fraction:

Microparticles are prepared by spray drying a formulation comprising HepB antigen and Trehalose using a Buchi 191 Mini Laboratory Spray Dryer. The resulting microparticles have a particle size of less than 5 µm.

'Nasal' Fraction:

20 Microparticles are prepared by spray drying a formulation comprising HepB antigen in a 20% w/v trehalose solution, using a Mobile Minor Niro Spray Dryer, fitted with an NT2 rotary atomiser rotating at 15,000 rpm. The resulting microparticles have a particle size of greater than 20 µm, with the majority of the particles being solid with a uniform size of around 50 µm. The microparticles of 25 the lung and nasal fraction are then blended to form one unit dose, and filled into a blister pack for subsequent administration via a dry powder inhaler device.

Example 2

A dry powder blend of microparticles is prepared as follows.

Immediate release formulation:

30 A solution of 20% (w/v) zinc insulin and 80% (w/v) Trehalose is prepared and spray dried using the Buchi Mini Laboratory Spray Dryer.

Microparticles are produced having a size less than 5 µm in diameter.

Controlled release formulation:

A formulation containing 25% w/w HPC (ex. Nippo Soda Co., Japan) 10% w/w recombinant human insulin and 65% w/w high molecular weight hyaluronic acid (ex. Genzyme) is prepared as follows. To 154 mg insulin is added 2.16 ml

5 0.05M HCl and swirled gently until dissolved. To this solution is added dropwise 0.14 ml 1M NaOH together with 165 ml purified water. This solution is then added to 96.25 ml of 0.4% w/v HPC solution and then 250 ml of a 0.4% w/v solution of high molecular weight hyaluronic acid is added and the mixture stirred until homogenous. Approximately 500 ml of this feedstock is spray dried at the

10 following settings: feed rate = 2.1 g/min, inlet temp = 130°C, outlet temp = 66°C, atomisation = 2-fluid nozzle, atomisation pressure = 2 barg, atomisation air flow rate = 21 l/min, drying air pressure = 1 barg, drying air flow rate = 5 l/sec.

The two formulations are then blended together to form the dual release system.

CLAIMS

1. A therapeutic composition in solid dose form comprising a mixture of first amorphous or non-crystalline microparticles comprising a bioactive agent and second amorphous or non-crystalline microparticles comprising the same or a different bioactive agent, wherein the first microparticles are from 0.1 to 10 μm in diameter and the second microparticles are from 10 to 1000 μm in diameter.
- 5 2. A composition according to claim 1, wherein the bioactive agent is an immunogen.
3. A composition according to claim 2, wherein the immunogen is an attenuated bacteria or virus, or an immunogenic peptide/protein.
- 10 4. A composition according to claim 2, wherein the immunogen is a viral particle.
5. A composition according to any preceding claim, wherein the first bioactive agent and/or the second microparticles comprise an adjuvant.
- 15 6. A composition according to any preceding claim, wherein the bioactive agents are the same.
7. A composition according to any preceding claim, wherein the second microparticles comprise, as a vehicle, a stabilising polyol.
8. A composition according to any of claims 1 to 6, wherein the second 20 microparticles comprise a HDC.
9. A device for delivering a bioactive agent to a patient comprising a composition according to any preceding claim.
10. A device according to claim 9, the device being a nasal insufflator.
11. A method for therapeutic treatment, comprising administering to a 25 mammal a composition according to any of claims 1 to 8.



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Application No: GB0228305.9

Examiner: Dr Simon Grand

Claims searched: 1-11

Date of search: 31 March 2004

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular reference
A,E	1	WO 03/032945 A1 (ELAN DRUG DELIVERY) See whole document.
A	1	WO 99/33853 A (QUADRANT HOLDINGS) See whole document

Categories:

<input checked="" type="checkbox"/> X Document indicating lack of novelty or inventive step	A Document indicating technological background and/or state of the art.
<input checked="" type="checkbox"/> Y Document indicating lack of inventive step if combined with one or more other documents of same category.	P Document published on or after the declared priority date but before the filing date of this invention.
<input checked="" type="checkbox"/> & Member of the same patent family	E Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^W :

Worldwide search of patent documents classified in the following areas of the IPC⁰⁷

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The following online and other databases have been used in the preparation of this search report

ONLINE: EPODOC, WPI, JAPIO.